

**SUPERFAST EVOLUTION OF BACTERIAL  
RESISTANCE TO BETA-LACTAM ANTIBIOTICS  
MEDIATED BY BACTERIAL DNA  
RECOMBINATION**

By

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This thesis is presented for the degree of Doctor of Philosophy

October 2020

# Certificate of Original Authorship

I, Le Zhang declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the IBMD, Faculty of Science at the University of Technology Sydney. This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literatures used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

This research is supported by an Australia Government Research Training Program Scholarship.

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Date: 06/10/2020

## **Acknowledgements**

After 3 years' study at University of Technology Sydney (UTS), I have completed my PhD thesis with the help of others. Firstly, I would like to thank my supervisor Prof. Dayong Jin for the valuable opportunity of PhD scholarship in Australia. From the beginning of my study, Prof. Jin has paid much energy and time to my research plan development. He has insights to foresee the trend of related research area and provided great ideas and suggestions for my research. I could not imagine how to complete my research without his guidance. Moreover, supervised by Prof. Jin, I have improved my ability on how to conduct the research project logically.

Meanwhile, I also would like to express my heartfelt thanks to my co-supervisors Prof. Elizabeth Harry, Prof. Antoine van Oijen, Dr. Yuen Yee Cheng, and Dr. Qian Peter Su. They helped me a lot with my experiment design, results discussion and we overcame the challenges in my research together. I thank them for devoting themselves to the development of my work.

Next, I would like to acknowledge all my colleagues who have given me help over the last several years. Thanks to the Zhiguang Zhou, Chaohao Chen, Yongtao Liu, Xuchen Shan, Baolei Liu, Hao He, Wei Ren, Ming Guan, Yinghui Chen, Jiayan Liao. Thank you for a lot of beneficial discussions and helps in both my study and life, and I appreciate your supports and friendship very much.

I give my deep appreciation to my family. I thank my parents for their moral support to my oversea PhD study, and my girlfriend for her thoughtfulness, understanding and sincere company.

Special thanks to our school manager Elizabeth Gurung Tamang, lab manager Katie McBean, and Ronald Shimmon for their technique support.

Finally, I would like to acknowledge the Australia Government and UTS for providing me with PhD scholarship and research opportunities.

## List of Publications

### Research papers:

- [1] Jin D\*, Xi P\*, Baoming Wang, **Zhang L**, Enderlein J, van Oijen AM. Nanoparticles for super-resolution microscopy and single-molecule tracking. Nature Method. 2018, 15: 415-423.
- [2] Tingting Chen, Anna B. Liu, Shili Sun, Nadim J. Ajami, Matthew C. Ross, Hong Wang, **Le Zhang**, Kenneth Reuhl, Koichi Kobayashi, Janet C. Onishi, Liping Zhao, Chung S. Yang\*. Green Tea Polyphenols Modify the Gut Microbiome in db/db Mice as Co-Abundance Groups Correlating with the Blood Glucose Lowering Effect. Molecular nutrition & food research. 2019, 63: 1801064.
- [3] **Le Zhang**, Qian Peter Su, Zhichao Kang, Yuen Yee Cheng, Yan Liao, Nural Cokcetin, Amy L. Bottomley, Qiongfang Li, Iain Duggin, Andrew Robinson, Elizabeth J. Harry, Antoine v. Oijen, Dayong Jin\*. Superfast bacterial evolution of resistance to  $\beta$ -lactam antibiotics mediated by bacterial DNA recombinases. Science. 2020. (Submitted).

## Abstract

The emergence of antibiotic resistance is a global problem. Many studies show that sub-lethal concentration of antibiotic exposure or transit exposure to antibiotics can induce the formation of persistence or tolerance; whereas, cyclic exposure (usually 8-17 days) of antibiotics promotes the accumulation of bacterial adaptive mutations in persisters towards the subsequent evolution of resistance. However, the antibiotics induce mutagenesis that damage bacterial DNA has been poorly understood. Notably, the induction of SOS response has always been believed to aid bacterial propagation defense against antibiotic lethality, which requires the activation of SOS-promoting *recA*. A recent study implicated the essential role of RecA in the evolution of resistance to fluoroquinolones antibiotics, but it is unclear whether this is a conserved mechanism of resistance in response to different antibiotic classes.

RecA has been considered as a drug target to suppress the induction of SOS response towards the evolution of resistance caused by the broad-spectrum fluoroquinolone antibiotics. Here, we report that single exposure of  $\beta$ -lactam antibiotics can trigger a superfast evolution of resistance in *recA* deletion *E. coli* strain, independent to the SOS response. This type of single exposure causes gene mutations on an uncharacterized gene *pinR*, and its encoded protein may be involved in DNA recombination. Moreover, single or intermittent treatment of  $\beta$ -lactam antibiotics fails to induce the resistance in the *pinR* deletion *E. coli* strain. This work highlights the antagonistic role among DNA recombinases in the emergence of antibiotic resistance, and demonstrates that loss of *recA* increases the rate of resistance to  $\beta$ -lactam antibiotics, but PinR is likely to be a novel drug target.

**Key words:** Antibiotic tolerance, heritable resistance, RecA, *pinR*, *ampC*,

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